

REMARKS

A check for \$690 for the requisite fee for a three-month extension of time (\$510) and the fee for filing a supplemental Information Disclosure Statement (\$180) accompanies this response. Any fees that may be due in connection with the filing of this paper or with this application may be charged to Deposit Account No. 06-1050. If a Petition for Extension of time is needed, this paper is to be considered such Petition.

Claim 73 is amended herein to replace the recitation "the solid support" with the recitation "a solid support." Claim 74 is amended herein to more distinctly claim the subject matter to state that the first nucleic acid is hybridized to the second nucleic acid to form a hybrid having a double stranded portion and a single stranded portion that includes the random terminal nucleotide sequence of between about 3-10 nucleotides in length. Claim 76 is amended to change the dependency of the claim to claim 75. Claim 127 is amended herein to more distinctly claim the subject matter by replacing the recitation "one of the four nucleic acid bases" with the recitation "a nucleic acid base." New claim 139 is added herein. Basis for claim 139 can be found throughout the specification (for example, see page 8, lines 5-7; and page 26, line 29 through page 27, line 2). No new matter is added.

REJECTION OF CLAIMS 70, 72, 73 AND 77-79 UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 70, 72, 73 and 77-79 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the patent applicant had possession of the claimed subject matter at the time of filing of the application. The Examiner alleges that the specification does not provide adequate support for the recitation "wherein the variable sequence is not at the 5' terminus or 3' terminus" in claim 70.

Applicant respectfully traverses the rejection.

RELEVANT LAW

The purpose behind the written description requirement is to ensure that the patent applicant had possession of the claimed subject matter at the time of filing of the application. *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). The manner in which the specification meets the requirement is not material; it may be met by either an express or an implicit disclosure.

A specification must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, *i.e.*, whatever is now

claimed. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ.2d 1111, 1117 (Fed. Cir. 1991). A written description requirement issue generally involves the question of whether the subject matter of a claim is supported by or conforms to the disclosure of an application as filed. The test for sufficiency of support in a patent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting *In re Kaslow*, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)) (see also, MPEP 2163.02).

An objective standard for determining compliance with the written description requirement is "does the description clearly allow persons of skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ.2d 1614, 1618 (Fed. Cir. 1989). The Examiner has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *In re Wertheim*, 541 F.2d 257, 265, 191 USPQ 90, 98 (CCPA 1976); *See also Ex parte Sorenson*, 3 USPQ.2d 1462, 1463 (Bd. Pat.App. & Inter. 1987).

Furthermore, the subject matter of the claim need not be described literally (*i.e.*, using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement. MPEP §2173.05(i) recites "that a lack of literal basis in the specification for a negative limitation may not be sufficient to establish a *prima facie* case for lack of descriptive support. *Ex parte Parks*, 30 USPQ2d 1234, 1236 (Bd. Pat. App. & Inter. 1993)."

CLAIM 70

Claim 70 is directed to an array of nucleic acid probes, where each probe has a double-stranded portion, a terminal single-stranded portion, and a random nucleotide sequence within the single-stranded portion, where the random sequence is not at the 5'-terminus or the 3'-terminus. Claims 72, 73 and 77-79 ultimately depend from claim 70 and are directed to various embodiments thereof.

ANALYSIS

Claims 70, 72, 73 and 77-79 are rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter that was not described in the specification. The Examiner contends that nowhere in the specification "is the random sequence defined as not at the 5' or 3' termini" (see Office Action, November 3, 2004, page 4). MPEP 2173.05(i) states that:

Any negative limitation or exclusionary proviso must have basis in the original disclosure. If alternate elements are positively recited in the specification, they may be explicitly excluded in the claims. See *In re Johnson*, 558 F.2d 1008, 1019, 194 USPQ 187, 196 (CCPA 1977) ("[the] specification, having described the whole, necessarily described the part remaining.").

The specification discloses arrays of probes having a double-stranded portion and a single-stranded portion, where the single-stranded portion includes a random nucleotide sequence. In some disclosed embodiments, the random nucleotide is at a terminus, such as the 3' terminus or the 5' terminus. In other embodiments, the random sequence is within the single-stranded sequence. For example, see page 6, lines 10-15, which recites:

Another embodiment of the invention is directed to methods for creating arrays of probes comprising the steps of synthesizing a first set of nucleic acids each comprising a constant sequence of length C at the 3'-terminus, and a **random sequence of length R at the 5'- terminus**, synthesizing a second set of nucleic acids each comprising a sequence complementary to the constant sequence of the first nucleic acid, and hybridizing the first set with the second set to form the array.

In addition, see for example, page 57, line 10 through page 58, line 13, which discloses an array of probes with the **random sequence at the 3' terminus**. Also see FIGS. 2A and 2B.

The specification also discloses arrays of probes where the random sequence is contained within the single-stranded portion. For example, see page 22, line 26 through page 23, line 7, which recites:

Another embodiment of the invention is directed to methods for creating arrays of probes comprising the steps of synthesizing an array of single-stranded nucleic acids each containing a constant sequence at the 3'-terminus, another constant sequence at the 5'-terminus, and a random internal sequence of length R flanked by the cleavage site(s) of a restriction enzyme (on one or both sides), synthesizing an array of primers each complementary to a portion of the constant sequence of the 3'-terminus, hybridizing the two arrays together to form hybrids, extending the sequence of each primer by polymerization using a sequence of the nucleic acid as a template, and cleaving the extended hybrids with the restriction enzyme to form an array of probes with a double-stranded portion at one terminus, a **single-stranded portion containing the random sequence at the opposite terminus**.

Preferably, the nucleic acids are each between about 10-50 nucleotides in length and R is between about 3-5 nucleotides in length. Any of the restriction enzymes which produce a 3'- or 5'-overhang after cleavage are suitable for use to make the array. [emphasis added]

Also, see page 6, lines 3-9, which recites:

One embodiment of the invention is directed to arrays of R^4 different nucleic acid probes wherein each probe comprises a double- stranded portion of length D, a terminal single-stranded portion of length S, and a **random**

nucleotide sequence within the single-stranded portion of length R. These arrays may be bound to solid supports and are useful for determining the nucleotide sequence of unknown nucleic acids and for the detection, identification and purification of target nucleic acids in biological samples. [emphasis added]

In addition, see page 6, lines 16-24, which teaches:

Another embodiment of the invention is directed to methods for creating arrays of probes comprising the steps of synthesizing a set of nucleic acids each containing a random internal sequence of length R flanked by the cleavage sites of a restriction enzyme, synthesizing a set of primers each complementary to a non-random sequence of the nucleic acid, hybridizing the two sets together to form hybrids, extending the sequence of the primer by polymerization using the nucleic acid as a template, and cleaving the hybrids with the restriction enzyme to form an array of probes with a double-stranded portion and a single-stranded portion and with **the random sequence within the single stranded portion**. [emphasis added]

Also, the Examiner states that the disclosure of the instant specification encompasses an array of probes including a random sequence anywhere within the single-stranded portion of the probes, including the termini (see Office Action, November 3, 2004, page 3). Hence, the specification provides alternate embodiments of the claimed array of probes each having a double-stranded portion, a single-stranded portion and a single-stranded random sequence: an embodiment where the random sequence is anywhere within the single-stranded region, an embodiment where the random sequence is at the 5'-terminus and an embodiment where the random sequence is at the 3'-terminus. Thus, a person of ordinary skill in the art would recognize that applicant had possession of an array of probes with a double-stranded portion and a single-stranded portion where the random sequence within the single stranded portion is at a terminus or is contained within the single-stranded region.

Because alternate elements are positively recited in the specification, they may be explicitly excluded in the claims (see MPEP §2173.05(i)). As amended, claim 70 is directed to an embodiment of an array of probes having a double-stranded portion and a single-stranded portion and a random sequence within the single-stranded portion but not at its terminus. Because the application discloses as elements a random sequence at the 3'-terminus and random sequence at the 5'-terminus, these elements may be explicitly excluded in the claims. Thus, applicant respectfully submits that there is no basis to conclude that a person skilled in the art at the time the application was filed would not have recognized the description of such an array in view of the disclosure of the application as filed.

Literal Basis

The Examiner contends that the specification does not specifically recite a random sequence "not at the 5' or 3' terminus" or define a random sequence as "not at the 5' or 3' termini" as now claimed. Applicant respectfully submits that the subject matter of the claim need not be described literally (*i.e.*, using the same terms or *in haec verba*) in order for the disclosure to satisfy the written description requirement. Applicant respectfully directs the Examiner to MPEP 2173.05(i), which recites:

Note that a lack of literal basis in the specification for a negative limitation may not be sufficient to establish a *prima facie* case for lack of descriptive support. *Ex parte Parks*, 30 USPQ2d 1234, 1236 (Bd. Pat. App. & Inter. 1993).

As discussed above, the amendment excludes alternative elements positively recited in the specification. Therefore, the amendment complies with the written description requirement and does not introduce new matter.

In view of the above remarks that make clear that the claims as amended were within the possession of the applicant at the time of filing the instant application, applicant respectfully requests that the rejection of claims 70, 72, 73 and 77-79 under 35 U.S.C. §112, first paragraph, be reconsidered and withdrawn.

REJECTION OF CLAIMS 73, 76, 127-133, 135, 137 AND 138 UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 73, 76, 127-133, 135, 137 and 138 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter.

This rejection is respectfully traversed.

RELEVANT LAW

Claims are not read in a vacuum but instead are considered in light of the specification and the general understanding of the skilled artisan. *Rosemount Inc. v. Beckman Instruments, Inc.*, 727 F.2d 1540, 1547, 221 USPQ 1, 7 (Fed. Cir. 1984), *Caterpillar Tractor Co. v. Berco, S.P.A.*, 714 F.2d 1110, 1116, 219 USPQ 185, 188 (Fed. Cir. 1983). A claim is not indefinite when one skilled in the art would understand all of the language in the claims when read in light of the specification.

35 U.S.C. §112, second paragraph requires only reasonable precision in delineating the bounds of the claimed invention. Claim language is satisfactory if it reasonably apprises those of skill in the art of the bounds of the claimed invention and is as precise as the subject matter

permits. *Shatterproof Glass Corp. v. Libby-Owens Ford Col.*, 758 F.2d 613, 624, 225 USPQ 634, 641 (Fed. Cir.), cert. dismissed, 106 S.Ct. 340 (1985).

THE CLAIMS

Claim 73 is directed to an embodiment of claim 70, where the probes of the array of claim 70 are fixed to a solid support selected from the group consisting of plastics, ceramics, metals, resins, gels, membranes, and chips.

Claim 76 is directed to an embodiment of claim 74, where the probes of the array of claim 76 are fixed to a solid support that is a two-dimensional or a three-dimensional matrix with multiple probe binding sites.

Claim 127 is directed to an array of nucleic acid probes, where each probe includes a single-stranded portion at one terminus, a double-stranded portion at the opposite terminus, and a variable nucleotide sequence within the single-stranded portion, where the probes are divided into four subsets, where for each subset, a nucleic acid base is selected and occupies a defined number of positions in each probe and all other bases except the selected base occupy the remaining positions. Claims 128-133, 135, 137 and 138 ultimately depend from claim 127 and are directed to various embodiments thereof.

ANALYSIS

CLAIM 73

Claim 73 is allegedly indefinite because the recitation "the solid support" lacks proper antecedent basis in claim 70. Applicant respectfully submits that this rejection is obviated by the amendment of claim 73 herein to recite "a solid support."

CLAIM 76

Claim 76 is allegedly indefinite because the recitation "the solid support" lacks proper antecedent basis in claim 74. Applicant respectfully submits that this rejection is obviated by the amendment of claim 76 herein, so that claim 76 depends from claim 75, which provides proper antecedent basis for the recitation "the solid support."

CLAIMS 132 and 133

Claims 132 and 133 are allegedly indefinite because the recitation "the solid support" lacks proper antecedent basis. Applicant respectfully submits that this rejection is obviated by the amendment of claims 132 and 133 herein to depend from claim 139. Claim 139 provides proper antecedent basis for the recitation "the solid support."

CLAIMS 127-133, 135, 137 and 138

Claim 127-133, 135, 137 and 138 are allegedly indefinite because the recitation "the four nucleic acid bases" lacks proper antecedent basis in the base claim and it is thus unclear which four bases are being described. Applicant respectfully submits that this rejection is obviated by the amendment of claim 127 herein, which replaces the recitation "the four nucleic acid bases" with the recitation –a nucleic acid base–.

THE REJECTION OF CLAIMS 70, 72, 74, 76-79, 92-94, 124 AND 136 UNDER 35 U.S.C. §102(e)

Claims 70, 72, 74, 76-79, 92-94, 124 and 136 are rejected under 35 U.S.C. §102(e) as anticipated by Deugau *et al.* (U.S. Patent No. 5,508,169) because Deugau *et al.* allegedly discloses an array of nucleic acid probes having a double-stranded portion and a single-stranded portion. The Examiner alleges that probes of Deugau *et al.* have a terminal nucleotide and the number of nucleotides between the terminus and the double-stranded region varies, and thus concludes that "the variable single stranded sequence would be interpreted as being not at the terminus, but instead between the terminus and the double stranded portion."

This rejection is respectfully traversed.

RELEVANT LAW

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. *In re Spada*, 15 USPQ2d 1655 (Fed. Cir., 1990), *In re Bond*, 15 USPQ 1566 (Fed. Cir. 1990), *Soundscriber Corp. v. U.S.*, 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir.), *cert. denied*, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention". *In re Lang*, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). Moreover it is incumbent on Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. *Lindemann Maschinen-fabrik GmbH v. American Hoist and Derrick Co.*, 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. An inherent property has to flow naturally from what is taught in a reference *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

THE CLAIMS

Claim 70 is directed to an array of nucleic acid probes, where each probe includes a double-stranded portion, a terminal single-stranded portion, and a random nucleotide sequence within the single-stranded portion, where the random sequence is not at the 5'-terminus or the 3'-terminus. Claims 72, 73 and 77-79 depend from claim 70 and are directed to various embodiments thereof.

Claim 74 is directed to an array of nucleic acid probes, where each probe includes a single-stranded first nucleic acid of about 15-25 nucleotides in length; a longer single-stranded second nucleic acid of about 20-30 nucleotides in length that includes a nucleotide sequence complementary to the first nucleic acid and a random terminal nucleotide sequence of between about 3-10 nucleotides in length; and an oligonucleotide of about 4-20 nucleotides in length that includes a random nucleotide sequence, where the first nucleic acid is hybridized to the second nucleic acid to form a hybrid having a double-stranded portion and a single-stranded portion that includes a random terminal nucleotide sequence of between about 3-10 nucleotides in length; and the oligonucleotide is ligated to the random nucleotide sequence of the second nucleic acid. Claims 75, 76, 92-94, 123, 124 and 136 depend from claim 74 and are directed to various embodiments thereof.

Claim 127 is directed to an array of nucleic acid probes, where each probe includes a single-stranded portion at one terminus, a double-stranded portion at the opposite terminus, and a variable nucleotide sequence within the single-stranded portion, where the probes are divided into four subsets, wherein for each subset, one of the four nucleic acid bases is selected and occupies a defined number of positions in each probe and all other bases except the selected base occupy the remaining positions. Claims 128-133, 135, 137 and 138 depend from claim 127 and are directed to various embodiments thereof.

Disclosure of Deugau *et al.*

Deugau *et al.* discloses indexing linkers that have single-stranded portions on both ends or on only one end. The reference discloses that the double-stranded portion can be at either the 3'-terminus or at the 5'-terminus. Deugau *et al.* discloses that the indexing linkers have a protruding single strand of a unique sequence of 3, 4, or 5 nucleotides, and that neither single-stranded end functions as a restriction endonuclease recognition site. Deugau *et al.* discloses that its single-stranded overhangs are produced by restriction endonucleases, which produce overhangs on each end of a fragment (col. 7, lines 48-60).

Differences between the claimed subject matter and the disclosure of Deugau *et al.*

1. As Directed to Claims 70, 72, 73 and 77-79

Deugau *et al.* does not disclose a probe that includes a random nucleotide sequence that is not at the 3'-terminus or the 5' terminus of the single-stranded portion. For example, Figure 2 of Deugau *et al.* illustrates a set of probes that have variable sequences at the terminus of the probes. Deugau *et al.* discloses that its single-stranded overhangs are produced by restriction endonucleases, which produce protruding overhangs on each end of a fragment (col. 7, lines 48-60). Because the restriction endonucleases produce terminal overhangs, the index linkers of Deugau *et al.* do not include a random sequence that is not terminal. Further, Deugau *et al.* discloses at col. 9, lines 29-42 that:

A preferred embodiment of this invention is a set of indexing linker strands comprising: (a) at least two single stranded first oligonucleotides each having a common identical sequence, and a unique sequence of a length selected from 3, 4 and 5 nucleotides selected from permutations and combinations of A, G, C & T nucleotides, at one end selected from a 3' end and a 5' end; and (b) a single stranded second oligonucleotide whose sequence is complementary to said common sequence such that, when hybridized with any one of the first oligonucleotides, a double stranded indexing linker molecule would result which includes a first end having a protruding single strand comprising said unique sequence and a second end having a protruding single strand of any number of nucleotides including zero. [emphasis added]

Thus, Deugau *et al.* does not disclose a random sequence within the single-stranded portion of its indexing linkers that is not at a terminus, and hence does not disclose every element of the claimed subject matter of claim 70 and its dependent claims. Therefore, because Deugau *et al.* does not disclose all elements of the claimed subject matter, Deugau *et al.* does not anticipate claims 70, 72, 73 and 77-79.

Terminal Nucleotide

The Examiner contends that "because the single-stranded portion of Deugau *et al.* has a terminal nucleotide and the number of nucleotides between the terminal nucleotide and the double-stranded portion varies, the variable single-stranded sequence would be interpreted as being not at the terminus, but instead between the terminus and the double-stranded portion. The applicant respectfully submits that claim 70 includes as an element a "random sequence" and not a "variable sequence." None of the pending claims include as an element the recitation "a variable sequence." It appears that the Examiner is contending that a "random sequence" is one that varies in length. The instant specification teaches that one embodiment of the claimed subject matter is directed to arrays of R^4 different nucleic acid probes wherein each probe comprises a double-stranded portion of length D, a terminal single-stranded portion of length S, and a random nucleotide sequence within the single-stranded portion of length R. In addition, the specification teaches, for example at page 11, lines 21-26, that

By way of example only, if the random portion consisted of a four nucleotide sequence ($R=4$) of adenine, guanine, thymine, and cystosine, the total number of possible combinations (4^R) would be 4^4 or 256 different nucleic acid probes. If the number of nucleotides in the random sequence was five, the number of different probes within the set would be 4^5 or 1,024. This becomes a very large number indeed when considering sequences of 20 nucleotides or more.

There is no disclosure in the instant specification that a "random sequence" is one "varying in length" as alleged by the Examiner. Further, such an interpretation is contrary to the teaching of Deugau *et al.* Deugau *et al.* teaches that its indexing linkers have single-stranded regions of the same length but of variable sequence. For example, see col. 9, lines 29-42, which recites:

A preferred embodiment of this invention is a set of indexing linker strands comprising: (a) at least two single stranded first oligonucleotides each having a common identical sequence, and a unique sequence of a length selected from 3, 4 and 5 nucleotides selected from permutations and combinations of A, G, C & T nucleotides, at one end selected from a 3' end and a 5' end; and (b) a single stranded second oligonucleotide whose sequence is complementary to said common sequence such that, when hybridized with any one of the first oligonucleotides, a double stranded indexing linker molecule would result which includes a first end having a protruding single strand comprising said unique sequence and a second end having a protruding single strand of any number of nucleotides including zero. [emphasis added]

In addition, Deugau *et al.* discloses at col. , lines that:

A set of indexing linker molecules according to this invention will include different indexing linker molecules having protruding single strands of the first end which comprise different sequences of nucleotides selected from possible combinations and permutations of the nucleotides A, C, G, and T. While the protruding first end single strands of indexing molecules in one set have different sequences, it is preferable that they be of the same length to facilitate use of the set to index fragments produced by cleavage by one endonuclease. It is preferable that the members of a set contain a double stranded portion which is identical for each member of the set. [emphasis added]

Thus, Deugau *et al.* discloses that the length of the "random sequence" is constant within a set of indexing linker strands, and not of varying length as suggested by the Examiner.

Terminal Nucleotide

It appears that the Examiner is urging that the terminal nucleotide in the set of indexing linkers of Deugau *et al.* is invariable. Applicant respectfully submits that the Examiner offers no support for this. There is no disclosure in Deugau *et al.* that the terminal nucleotide of its indexing linkers does not vary or is in some manner held constant. Thus, there is no support within the disclosure of Deugau *et al.* that would support an interpretation of the "random sequence" of Deugau *et al.* as being not at the terminus but instead between the terminus and the double-stranded portion of the indexing linker of Deugau *et al.*, as alleged by the Examiner. To the contrary, Deugau *et al.* discloses that its single-stranded overhangs are produced by restriction endonucleases, which produce protruding overhangs on each end of a fragment. Further, Deugau *et al.* discloses that its comprehensive panel of indexing linkers contains all possible combinations and permutations of the nucleotides A, C, G and T. Thus, Deugau *et al.* does not disclose a random sequence within the single-stranded portion of its indexing linkers that is not at a terminus, and hence does not disclose every element of the claimed subject matter of claim 70 and its dependent claims. Applicant respectfully requests that the rejection be reconsidered and withdrawn.

2. As Directed to Claims 74-76, 92-94, 123, 124 and 136

The Examiner contends that the pending claim 74 and its dependent claims do not require a single-stranded region of 7 to 30 nucleotides, because the claims allegedly include a first sequence of 15-25 hybridized to a second, longer sequence of 20-30 where the second sequence is ligated to an oligomers of 4 to 20 nucleotides. The Examiner contends that there are many examples where the claimed array of probes do not have to include probes having a single-stranded region of 7 to 30 nucleotides. As an example, the Examiner contends that the first sequence can be 25 nucleotides, the second sequence can be 26 nucleotides and the oligonucleotide can be 4 nucleotides, and when the oligo is ligated to the single-stranded region, the resulting single-stranded region is 5 nucleotides in length.

Applicant respectfully submits that claim 74 claims as subject matter an array of probes each of which includes a first sequence of 15-25 nucleotides and a second, longer sequence of 20-30 nucleotides that includes a random terminal nucleotide sequence of between about 3-10 nucleotides in length, and an oligonucleotide of 4 to 20 nucleotides, where the first nucleic acid is hybridized to the second nucleic acid to form a hybrid having a double stranded portion and a single stranded portion that includes a random terminal nucleotide sequence of between about 3-10 nucleotides in length and the oligonucleotide is ligated to the random nucleotide sequence of the second nucleic acid. Thus, the claimed subject matter is directed to an array of probes each having a double-stranded region and a single-stranded region of about 3-10 nucleotides in length to which an oligonucleotide of 4 to 20 nucleotides is ligated. Thus, the claimed arrays include probes having a single-stranded region of about 7 nucleotides (3 nucleotides from the second longer nucleotide sequence and 4 from the ligated oligonucleotide) and up to about 30 nucleotides (10 nucleotides from the second longer nucleotide sequence and 20 from the ligated oligonucleotide).

Deugau *et al.* does not disclose an array of nucleic acid probes, where each probe includes a double-stranded portion and a single-stranded portion of greater than 5 nucleotides. As discussed above, Deugau *et al.* discloses that its indexing linkers are terminated by overhangs produced by cleavage with restriction endonucleases and are of a length of 3, 4, or 5 nucleotides. Deugau *et al.* does not disclose an array of probes where each probe has a double-stranded region and a single-stranded region, where the single-stranded region is greater than 5 nucleotides in length as instantly claimed. Hence, Deugau *et al.* does not disclose every element of the claimed subject matter of claim 74 and its dependent claims.

Thus, because Deugau *et al.* does not disclose all elements of the claimed subject matter, Deugau *et al.* does not anticipate claims 74-76, 92-94, 123, 124 and 136.

REJECTION OF CLAIMS 73 AND 123 UNDER 35 U.S.C. §103(a)

Claim 73 and 123 are rejected under 35 U.S.C. §103(a) as being unpatentable over Deugau *et al.* in view of Brenner *et al.* (*Proc. Natl. Acad. Sci. USA*, 1989, 86:8902-8906) because Deugau *et al.* allegedly teaches every element of the claimed subject matter except the specific means by which the probes are immobilized, but Brenner *et al.* allegedly cures this defect. The Examiner alleges that Brenner *et al.* teaches that biotin/streptavidin provides a versatile means of capture immobilization.

This rejection is respectfully traversed.

RELEVANT LAW

In order to set forth a *prima facie* case of obviousness under 35 U.S.C. §103: (1) there must be some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (*ACS Hospital Systems, Inc. v. Montefiore Hospital*, 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)) and (2) the combination of the cited references must actually teach or suggest the claimed invention. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. *Ex parte Gerlach*, 212 USPQ 471 (Bd. APP. 1980). Obviousness is tested by "what the combined teachings of the references would suggest to those of ordinary skill in the art" *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination (*ACS Hosp. Systems, Inc. v Montefiore Hosp.* 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)).

"To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" *W.L. Gore & Associates, Inc. v. Garlock Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

THE CLAIMS

Claim 73 depends from claim 70, and claim 123 depends from claim 74. Claim 73 and claim 123 are directed to an embodiment where the probes are fixed to a solid support by conjugating to a coupling agent selected from the group consisting of antibody/antigen,

biotin/streptavidin, *Staphylococcus aureus* protein A/IgG antibody F_c fragment, nucleic acid/nucleic acid binding protein, and streptavidin/protein A chimeras.

Teachings of the Cited References

Deugau *et al.*

See related section above.

Brenner *et al.*

Brenner *et al.* teaches a fluorescent DNA sequence fingerprinting procedure that couples band separation with sampled nucleotide sequencing (page 8902, right column, lines 11-14). The reference teaches cleaving DNA using endonuclease followed by electrophoresis and analysis by fluorescent emissions (paragraph bridging pages 8902-8903). Brenner *et al.* teaches that following specific cleavage using any restriction enzyme, biotin can be attached to each primary cleavage end by adding biotinylated nucleotides (page 8904, left column, second full paragraph).

ANALYSIS

It is respectfully submitted that the Examiner has failed to set forth a case of *prima facie* obviousness for the following reasons.

The combination of teachings of Deugau *et al.* with the teachings of Brenner *et al.* does not result in the instantly claimed arrays.

Claim 73

As discussed above in the traverse of the §102(e) rejection, Deugau *et al.* does not teach or suggest an array of nucleic acid probes having a random sequence within the single-stranded portion that is not at the 5'-terminus or the 3'-terminus. Brenner *et al.* does not cure this defect.

Brenner *et al.* teaches a DNA fingerprinting technique that includes primary cleavage of the DNA, attaching biotin to both ends, performing a secondary cleavage, attaching the biotinylated ends to beads, labeling the ambiguous overhangs with fluorescent nucleotide-specific terminators, and eluting the labeled strands for electrophoresis (see page 8904, paragraph bridging the left and right columns and Figure 4). Brenner *et al.* does not teach or suggest a probe having a double-stranded region, a terminal single-stranded region and a random sequence within the single-stranded region that is not at the 5'-terminus or the 3'-terminus. As shown in Figure 4, after specific cleavage, all of the resulting fragments have a single-stranded region on both ends (page 8904). Brenner *et al.* does not teach or suggest including a non-terminal random sequence within the single-stranded region. Hence,

even if, arguendo, Brenner *et al.* teaches coupling oligonucleotides to a solid support using biotin, the combination of the teachings of Deugau *et al.* and Brenner *et al.* does not teach or suggest every element of claim 73.

Neither Deugau *et al.* nor Brenner *et al.*, individually or in combination, teaches or suggests an array of nucleic acid probes, where each probe includes a double-stranded portion, a terminal single-stranded region and a random nucleotide sequence within the single-stranded portion that is not at the terminus. Thus, the combination of teachings of Deugau *et al.* and Brenner *et al.* does not result in the instantly claimed arrays of claim 73. Therefore, because the combination of teachings of the references does not result in the instantly claimed subject matter, the Examiner has failed to set forth a *prima facie* case of obviousness.

Claim 123

As discussed above in the traverse of the §102(e) rejection, Deugau *et al.* does not teach or suggest an array of probes where each probe has a double-stranded region and a single-stranded region, where, because a terminal nucleotide sequence of between 3-10 nucleotides is ligated to an oligonucleotide of about 4-20 nucleotides, the single-stranded region has a length greater than 5 nucleotides.

Brenner *et al.* does not cure this defect. Brenner *et al.* teaches a DNA fingerprinting technique that includes primary cleavage of the DNA using restriction enzymes or other methods of specific cleavage, attaching biotin to both ends, performing a secondary cleavage, attaching the biotinylated ends to beads, labeling the ambiguous overhangs with fluorescent nucleotide-specific terminators, and eluting the labeled strands for electrophoresis (see page 8904, paragraph bridging the left and right columns and Figure 4). Brenner *et al.* teaches single-stranded ambiguous overhangs of 1, 2 and 4 nucleotides in length (see Fig 1., page 8903). Brenner *et al.* does not teach or suggest a probe having a double-stranded region, and a terminal single-stranded region of between about 7 to about 30 nucleotides in length. Hence, even if, arguendo, Brenner *et al.* teaches coupling oligonucleotides to a solid support using biotin, the combination of the teachings of Deugau *et al.* and Brenner *et al.* does not teach or suggest every element of claim 123.

Neither Deugau *et al.* nor Brenner *et al.*, individually or in combination, teaches or suggests an array of nucleic acid probes, where each probe includes a single-stranded first nucleic acid of about 15-25 nucleotides in length; a longer single-stranded second nucleic acid of about 20-30 nucleotides in length that includes a nucleotide sequence complementary to the

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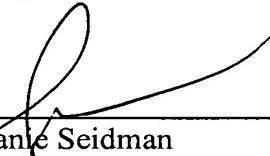
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first nucleic acid and a random terminal nucleotide sequence of between about 3-10 nucleotides in length; and an oligonucleotide of about 4-20 nucleotides in length that includes a random nucleotide sequence, where the first nucleic acid is hybridized to the second nucleic acid to form a hybrid having a double-stranded portion and a single-stranded portion including a random terminal nucleotide sequence of between about 3-10 nucleotides in length; and the oligonucleotide is ligated to the random nucleotide sequence of the second nucleic acid. Thus, the combination of teachings of Deugau *et al.* and Brenner *et al.* does not result in the instantly claimed array of claim 123. Therefore, because the combination of teachings of the references does not result in the instantly claimed subject matter, the Examiner has failed to set forth a *prima facie* case of obviousness.

* * *

In view of the amendments and remarks herein, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,



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